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Brief Clinical Report

Hemihypertrophy, Hemimegalencephaly, and Polydactyly

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We present clinical and neuropathological details of a patient with hemihypertrophy and hemimegalencephaly who may have Proteus syndrome. The observation of polysyndactyly in the case indicates either that polysyndactyly is a rare manifestation in Proteus syndrome, or that a separate condition, mimicking Proteus syndrome and pursuing a similar clinical course, might exist.

KEY WORDS: proteus syndrome, polysyndactyly, hemimegalencephaly, hemihypertrophy

INTRODUCTION

Recognising the variable nature of the phenotype, Wiedemann et al. [1983] suggested the name Proteus syndrome for the condition of hemihypertrophy, subcutaneous hamartomata, macrodactyly, and skin pigmentary disturbance which they reported in four cases. Several subsequent reports have emphasised the unpredictability of the nature and extent of the growth disturbance seen in this condition as well as extending the phenotype to include such signs as gyriform hyperplasia of the skin, skull exostoses, lymphangiomata, lipomata, and haemangiomata among many other less commonly recorded anomalies [Gorlin et al., 1990; Clark et al., 1987]. A hallmark of Proteus syndrome is the phenotypic variability but it is this same characteristic which defies the delineation of the condition. The problem is that, being sporadic, the spectrum of the phenotype cannot be determined and there is a consequent danger of stretching the limits of the syndrome beyond its biological boundary. Recognising this background we present details of a child, initially thought to represent an unusual oro-facio-digital syndrome, but whose subsequent progress was more typical of Proteus syndrome, although the precise diagnosis in this case remains unclear.

CLINICAL REPORT

The patient, a boy, was born spontaneously at 34 weeks of gestation. Pregnancy had progressed normally until 33 weeks when an ultrasound scan documented mild to moderate bilateral hydronephrosis and polyhydramnios. There had been a single recording of maternal hyperglycaemia during the pregnancy but glycosuria had not developed and a glucose tolerance test 6 weeks post partum was normal. Birth weight was 2.98 kg (90th centile for gestational age). Hypoglycaemia and seizures developed neonatally and responded rapidly to intravenous glucose. A blood count on day 4 showed neutropenia and CSF examination showed an elevated white cell count. Although appropriate cultures were negative, and no evidence of infection was subsequently identified, antibiotic treatment for a possible meningitis was initiated. A single episode of hypocalcaemia was also recorded (1.2 mmol/L) and treated. Meanwhile his respiratory function was causing concern and he was transferred to Great Ormond Street Hospital for Sick Children.

Clinical examination showed post-axial polydactyly of the hands with total syndactyly of fingers 3 and 4 bilaterally (Figs. 1, 2). Radiological examination additionally showed bony union of the terminal phalanges of digits 3 and 4 on the left side. The right foot had a wide space between digits 1 and 2, cutaneous syndactyly between 2 and 3, in addition to post-axial polydactyly (Fig. 3). The left foot showed fixed talipes but without polydactyly. Intraoral examination showed a small swelling on the dorsal surface of the tongue and the gums on the right side seemed to have some additional frenula, although in retrospect this may have been a misinterpretation of hypertrophy which subsequently became more evident. Additionally there was widespread cutis marmorata but no evidence of linear sebaceous naevus or of cutaneous haemangiomata.

CT brain examination at 10 days showed that the right ventricle was relatively large with poor differentiation between the white and grey matter. It was concluded that he had hemimegalencephaly. Hydrocephalus developed and ventriculo-peritoneal shunting was required. On review at age 5 months, right hemi-

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Fig. 1. Postaxial polydactyly and 3/4 syndactyly of the left hand.

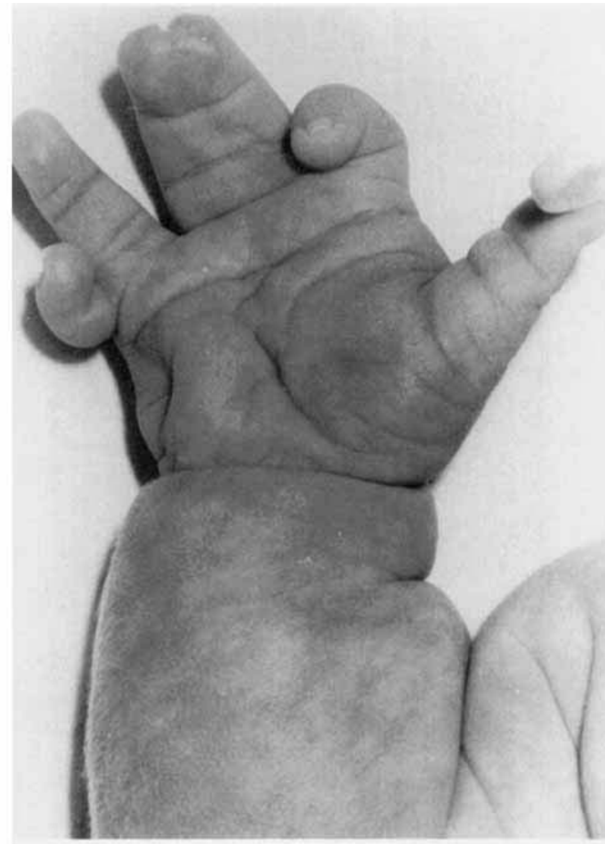

Fig. 2. Postaxial polydactyly and 3/4 syndactyly of the right hand.

hypertrophy had developed and was progressing rapidly. The face, arm, and leg all showed evidence of involvement in the hypertrophic process (Fig. 4).

Re-examination at age 9 months showed that the hemihypertrophy had continued to progress. The head circumference was on the 90th centile, while his weight was just above the 3rd centile. Although his pupils reacted to light, he did not fix or follow. He reacted normally to sound. Development was thought to be appropriate to the 6 month level. The patient's mother pointed out that there appeared to be some jerks and it is possible that these were myoclonic in nature. All other investigations, including blood and skin chromosomes were normal.

At the age of 10 months the patient had a grand mal seizure and died suddenly. Autopsy showed nonspecific hyperlobulation of the lungs and liver and bilateral hydronephrosis. All other abnormalities related to the brain. The fixed brain weighed 1,488 gm (normal for 21 months = 1,120 gm [Dekaban, 1978] or 1,060 gm [Coppoletta and Wolbach, 1933]) and was strikingly asymmetric (Fig. 5), with right hemimegalencephaly. The right hemisphere weighed 869 gm. By comparison the left hemisphere weighed 466 gm and the hindbrain 153 gm. Each lobe on the right appeared bigger than the corresponding left sided lobe and, while the surface on the left hemisphere was unremarkable, the right hemisphere had rather broad convulations over the vertex frontally, and an uneven cobbled surface over the lateral face of the frontal and temporal lobes and around the Sylvian fissure. All the cranial nerves, including both olfactory nerves were normal, except for the optic nerves, where the left had almost twice the cross sectional area of the right. Optic tracts were equal.

On coronal sectioning the left cerebral hemisphere was normal in all respects except for modest dilatation of the body of the lateral ventricle with squaring off of the frontal horn. The right cerebral hemisphere was excessively large, its lateral ventricle overlarge and abnormally shaped, appearing to extend in the superior-inferior direction. In addition, the superior angle was narrowed to a sharp point and the occipital horn showed several pointed recesses or small diverticula. Basal grey nuclei and mesial temporal structures on the right were normal, and symmetrical with those on the left. The central white matter was bulky but appropriately myelinated; capsule and commissures were well formed. The cortical ribbon anteriorly appeared normal, but around the insula extending into nearby frontal and parietal regions and the lateral part of the temporal lobe the cortical ribbon was irregular (Fig. 6) with an undulating margin to subjacent white matter, suggesting polymicrogyria. The occipital lobe and medial and superior parts of the parietal lobes had a normal cortical ribbon, but abnormally coarse convolutions. The cerebellar hemispheres also appeared asymmetric, the

Fig. 3. Postaxial polydactyly and 2/3 syndactyly of the left foot.

Fig. 4. Marked right facial hypertrophy.

right weighed 82 gm and the left 55 gm, although the overall surface folial patterns were normal on both sides. On gently separating the hemispheres the vermis was clearly seen. From the inferior surface of the right hemisphere there was a protruding herniation of the tonsil (Fig. 7), a bifid tongue of tissue extending 2.5 cm below the olivary bulge to about C3 level (Chiari type I malformation). Horizontal sections of the brainstem demonstrated further asymmetry, the right basis pontis and medullary pyramid being considerably larger than the left.

Histologically there were extensive migration defects in the right hemisphere: widespread polymicrogyria of the more common unlayered variety (Fig. 8) and neuronal heterotopia in the molecular layer (microdysgenesis), in the leptomeninges, and within the white matter both as a diffuse scattering of neurons and as nodular heterotopia. No histological abnormalities were detectable in the cerebellum but the hindbrain asymmetry was associated with an excessively large right corticospinal tract (Fig. 9). The enlargement of the left optic nerve was the result of a loosening of the individual nerve bundles, and an additional hamartomatous outer layer of uniform non-neoplastic astrocytes which first appeared just distal to the chiasm.

DISCUSSION

The causes of hemihypertrophy are multiple but, in the context of a syndrome diagnosis, the conditions with which it is most readily associated include Proteus syndrome, Wiedemann-Beckwith syndrome, Klippel-Trenaunay-Weber syndrome, and linear sebaceous naevus syndrome. In this case the absence of characteristic skin findings are strongly against possible diagnoses of Klippel-Trenauny-Weber and linear sebaceous naevus syndromes. Likewise the polysyndactyly and hemimegalencephaly in this patient are beyond the spectrum of Wiedemann-Beckwith syndrome, although the transient neonatal hypoglycaemia would be characteristic of this condition. However, the absence of any other manifestations consistent with Wiedemann-Beckwith syndrome, allied to the subsequent clinical course suggest that the diagnosis lies outside the Wiedemann-Beckwith range. The rapidly progressive nature of the hypertrophy seen in this patient is reminiscent of that recorded in other patients with Proteus syndrome. Although central nervous system involvement in Proteus syndrome is unusual, it is not unprecedented. Rizzo et al. [1990] reported a case in whom the CT scan showed marked asymmetry against a clinical background of mental retardation and seizures and led the authors to speculate that the underlying pathology might be that of hemimegalencephaly. In addition to the asymmetry, this patient had deep plantar creases and a linear epidermal naevus. Mayatepek et al. [1989] reported a case of Proteus syndrome with cortical atrophy and agenesis of the corpus callosum, as well as more typical findings of hemihypertrophy, macrodactyly, hamartomata, and pigmented

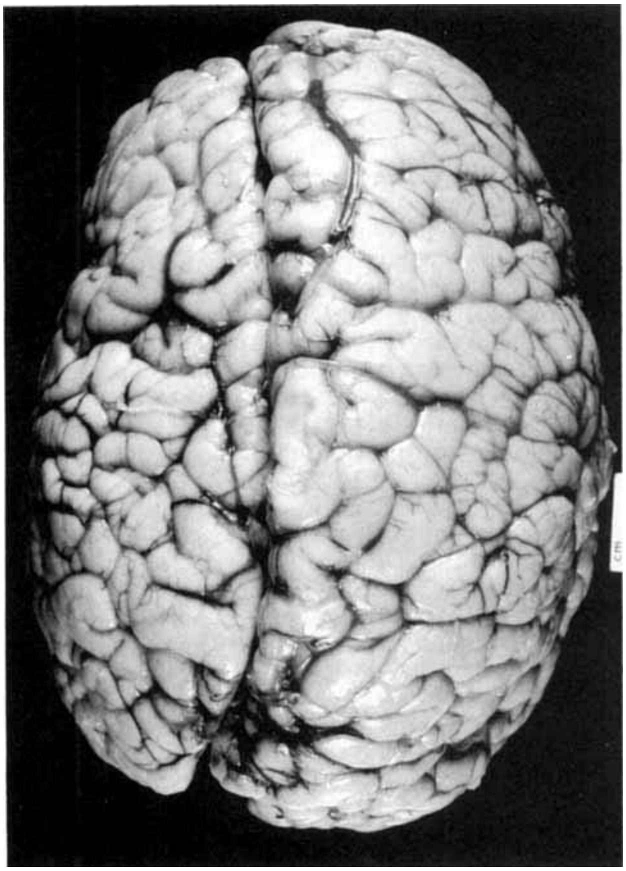

Fig. 5. The brain viewed from above shows marked asymmetry between the two hemispheres.

nevi. Griffiths et al. [1994] cited three cases with Proteus syndrome and reported radiological details of the macrocephaly which included hypoplastic corpus callosum, schizencephaly and white matter calcification in the three Proteus cases included in the report. Dean et al. [1990] drew attention to three cases with facial hemihypertrophy, ipsilateral hemimegalencephaly, and apparent ipsilateral hydrocephalus. Other clinical signs of Proteus syndrome were absent in these children and the authors reported their observations under the title of "cranial hemihypertrophy." None of these reports has been helpful in clarifying the neuropathological basis of the brain hemihypertrophy.

The clinical history of hydrocephalus and sudden death in our subject is perhaps not surprising in view of the presence of chronic tonsillar herniation or Chiari type I malformation. Hydrocephalus is a well-recognised presentation of this condition, though usually beginning later in life, but sudden unexpected death in infancy [Friede and Roessmann, 1986] and sleep apnoea [Ruff et al., 1987] have also been reported. The neuropathological findings are neither unique nor causally specific. The term hemimegalencephaly is broadly employed nowadays to denote asymmetric enlargement of one cerebral hemisphere, which may be associated with a variety of conditions including various migration or maturation disorders such as cortical

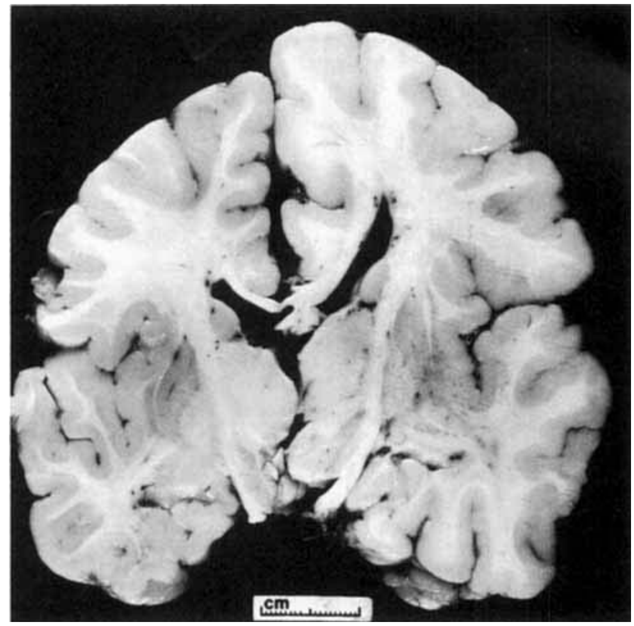

Fig. 6. Coronal slice throgh the frontal lobes demonstrating that the larger right hemisphere has an irregular cortical ribbon, particularly the frontal and insular cortex, but normal basal ganglia and thalamus.

and white matter dysplasia, pachygyria, and polymicrogyria [Damsbska et al., 1984; Barkovitch and Chuang, 1990; DeRosa et al., 1992; Harding, 1992]. Polymicrogyria itself, presently considered a disorder either of neuroblast migration or post-migrational organisation, is a well-known consequence of mid-gestational hypoxic or viral insult, but may occasionally be familial or associated with inborn errors [Harding, 1992].

Other reports have also instanced CNS involvement in Proteus syndrome. Goodship et al. [1991] reported a case with facial hypertrophy, hemimegalencephaly and a linear sebaceous naevus. The radiological manifestations of this cases were included in the report by Griffiths et al. [1994]. Costa et al. [1985] drew attention

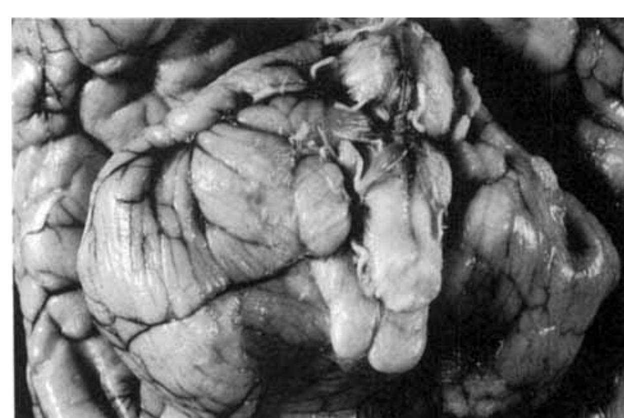

Fig. 7. Hindbrain viewed from below and in front: note the bifid tongue of herniated cerebellar tonsils.

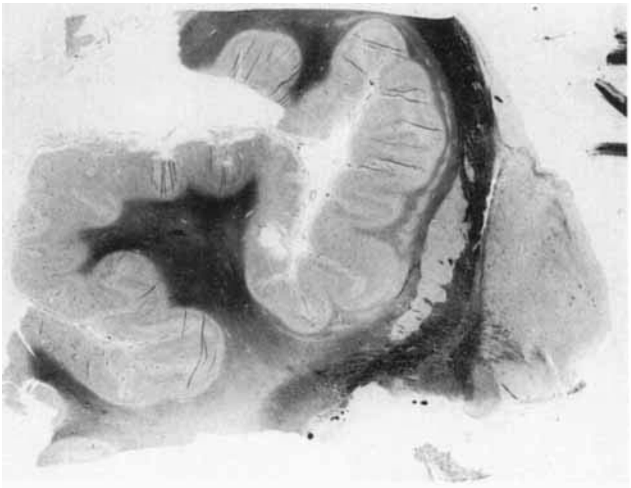

Fig. 8. Histological preparation of the insular cortex showing extensive polymicrogyria with interruption of the cortical ribbon by perpendicular and branching fingers of cell-poor molecular layer. Luxol Fast Blue-Nissl × 2.25.

to a case with an IQ of 75 and some ventriculomegaly with CT scan asymmetry, while Hornstein et al. [1987] reported on a patient with developmental delay. Likewise the report of Cohen and Hayden [1979], the first report of Proteus syndrome, detailed two children who were mentally handicapped, one of whom had an air encephalogram which showed hydrocephalus involving one lateral ventricle as well as the third and fourth ventricles. Some of these cases, especially where asymmetry was observed, may have had hemimegalencephaly. It should be emphasised that these cases are somewhat atypical in that many patients with Proteus syndrome have normal intelligence [Clark et al., 1987].

The patient we report is atypical of Proteus syndrome, not only for the CNS involvement, but also with respect to the polysyndactyly. In a review of 55 cases of Poteus syndrome, Hotamisligil [1990] identified syndactyly in three patients and polydactyly in only one

Fig. 9. Horizontal section through the medulla showing asymmetric pyramids. Luxol Fast Blue-Nissl × 3.3.

[Stevenson and Saul, 1982]. However the polydactyly, which was postaxial, was a familial trait in the latter and a convincing report of polydactyly in Proteus syndrome is still lacking. Hand abnormalities similar to those we now describe have been documented in Pallister-Hall syndrome [Thomas et al., 1994] but the presence of hemihypertrophy and the absence of the characteristic hypothalamic tumour in our case make Pallister-Hall syndrome unlikely. In addition, hemimegalencephaly is not characteristic of that condition. The small tongue hamartoma and the additional frenula initially led to a suggested diagnosis of oro-facio-digital syndrome, but the rapid progress of the hypertrophy was more typical of Proteus syndrome. Additionally, the frenula became less evident as they were incorporated into the unilateral gum hypertrophy which subsequently developed. It also needs to be emphasised that the patient had neither vascular skin nevi, nor linear sebaceous nevi, often found in Proteus syndrome, so that other diagnostic possibilities had to be considered.

One possibility was that the phenotype represented two separate pathological entities, one of which might explain the hemihypertrophy and the other of which might be responsible for the polysyndactyly. Diabetic embryopathy has been known to cause polydactyly on rare occasions. In this case the evidence for gestational diabetes is minimal and the likelihood of diabetes mellitus as a contributory factor to the malformations reported is minimal. An alternative possibility is that the patient may represent a new condition in which a single underlying mutation might account for all of his manifestations, including hemihypertrophy and polysyndactyly. Finally, it may be that the patient truly represents Proteus syndrome associated with polysyndactyly not hemimegalencephaly, both rare of the syndrome. Further reports will this issue.

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